wherein

1. Use of compounds having matrix metalloprotease inhibitory activity and the generalized formula:

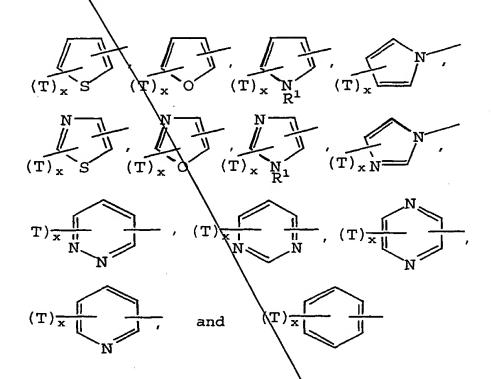
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 $(T)_X$ A-B-D-E-CO<sub>2</sub>H

(a) (T) A represents a substituted or unsubstituted aromatic or heteroaromatic moiety selected from the group consisting of:



wherein R<sup>1</sup> represents H or alkyl of 1 - 3 carbons; and

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each T represents a substituent group, independently selected from the group consisting of:

- \* the halogens -F, -Cl, -Br, and -I;
- alkyl of 1 10 carbons;

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haloalkyl of 1 - 10 carbons;

- \* \ haloalkoxy of 1 10 carbons;
- alkenyl of 2 10 carbons;
- \* \alkynyl of 2 10 carbons;
- \* -(CH<sub>2</sub>)<sub>p</sub>Q, wherein

p is 0 or an integer 1 - 4,

- \* -alkenyl-Q, wherein
  - said alkenyl moiety comprises 2 4 carbons, and
- -alkynyl-Q, wherein

said alkynyl moiety comprises 2 - 7 carbons; and

is selected from the group consisting of aryl of 6 - 10 carbons, heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, -CN, -CHO, -NO2, -CO2R<sup>2</sup>, -OCOR<sup>2</sup>, -SOR<sup>3</sup>, -SO2R<sup>3</sup>, -CON(R<sup>4</sup>)<sub>2</sub>, -SO2N(R<sup>4</sup>)<sub>2</sub>, -C(O)R<sup>2</sup>, -N(R<sup>4</sup>)<sub>2</sub>, -N(R<sup>2</sup>)COR<sup>2</sup>, -N(R<sup>2</sup>)CO2R<sup>3</sup>, -N(R<sup>2</sup>)CON(R<sup>4</sup>)<sub>2</sub>, -CHN<sub>4</sub>, -OR<sup>4</sup>, and -SR<sup>4</sup>;

wherein

R<sup>2</sup> represents H;

alkyl of 1 - 6 carbons;

aryl of 6 - 10 carbons;

heteroaryl comprising 4 - 9 carbons and at least one N, O, or S

heteroatom; or

arylalkyl in which the aryl portion contains 6 - 10 carbons and

the alkyl portion contains 1 - 4 carbons; or

heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9

carbons and at least one N, O, or S heteroatom and the alkyl

portion contains 1 - 4 carbons;

 $R^3$ 

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represents alkyl of 1 - 4 carbons;
aryl of 6 - 10 carbons;
heteroaryl comprising 4 - 9 carbons and at least one N, O, or S
heteroatom; or
arylalkyl in which the aryl portion contains 6 - 10 carbons and
the alkyl portion contains 1 - 4 carbons; or
heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9
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carbons and at least one N, O, or S heteroatom and the alkyl

R<sup>4</sup> represents H; alkyl of 1 -\12 carbons; aryl of 6 - 10 carbons;

portion contains 1 - 4 carbons;

heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;

arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons;

heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

alkenyl of 2 - 12 carbons; alkynyl of 2 - 12 carbons;

 $-(C_qH_{2q}O)_rR^5$  wherein q is 1-3; r is 1 - 3; and  $R^5$  is H provided q is greater than 1, or alkyl of 1 - 4 carbons, or phenyl;

alkylenethio terminated with H, alkyl of 1-4 Carbons, or phenyl;

alkyleneamino terminated with H, alkyl of 1-4 carbons, or phenyl;

-(CH2)<sub>S</sub>X wherein s is 1 - 3 and X is halogen;

 $-C(O)OR^2$ ; or

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 $-C(O)R^{2};$ 

and with the provisos that a) when two R<sup>4</sup> groups are situated on a nitrogen, they may be joined by a bond to form a heterocycle, and b) unsaturation in a moiety which is attached to Q or which is part of Q is separated from any N, O, or S of Q by at least one carbon atom, and

x is 0, 1, or 2;

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(b) B represents a bond or an optionally substituted aromatic or heteroaromatic ring containing 0-2 substituents T, which substituents T may independently have the meaning specified under (a), the B rings being selected from the group consisting of: wherein R<sup>1</sup> is as defined above; **(**c) D represents =NN(R 2)2 in which  $\mathbb{R}^2$  is defined as above and each  $\mathbb{R}^2$  may be the same or different;

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E represents a chain of n carbon atoms bearing m substituents R<sup>6</sup>, wherein said R<sup>6</sup> groups are independent substituents, or constitute spiro or nonspiro rings in which a) two groups R<sup>6</sup> are joined, and taken together with the chain atom(s) to which said two R<sup>6</sup> group(s) are attached, and any intervening chain atoms, constitute a 3 - 7 membered ring, or b) one group R<sup>6</sup> is joined to the chain on which said one group R<sup>6</sup> resides, and taken together with the chain atom(s) to which said R<sup>6</sup> group is attached, and any intervening chain atoms, constitutes a 3 - 7 membered ring; and wherein n is 2 or 3;

m is an integer of 1 - 3;

each group R<sup>6</sup> is independently selected from the group consisting of:

- \* fluorine;
- \* hydroxyl, with the proviso that a single carbon may bear no more than one hydroxyl substituent
- \* alkyl of 1 10 carbons;
- \* aryl of 6 10 carbons;
- \* heteroaryl comprising 4 9 carbons and at least one N, O, or S heteroatom;
- \* arylalkyl wherein the aryl portion contains 6 10 carbons and the alkyl portion contains 1 8 carbons;
- \* heteroaryl-alkyl wherein the heteroaryl portion comprises 4 9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 8 carbons;
- \* alkenyl of 2 10 carbons;
- \* aryl-alkenyl wherein the aryl portion contains 6 10 carbons and the alkenyl portion contains 2 5 carbons;

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heteroaryl-alkenyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkenyl portion contains 2 -5 carbons;

- \* alkynyl of 2 10 carbons;
- \* aryl-alkynyl wherein the aryl portion contains 6 10 carbons and the alkynyl portion contains 2 5 carbons;
- heteroaryl-alkynyl wherein the heteroaryl portion comprises 4 9 carbons and at least one N, O, or S heteroatom and the alkynyl portion contains 2 5 carbons;
- \* -(CH<sub>2</sub>)<sub>t</sub>R<sup>7</sup> wherein

  t is 0 or an integer of 1 5; and

  R<sup>7</sup> is selected from the group consisting of

DIMETER DICE

and corresponding heteroaryl moieties in which the aryl portion of an aryl-containing R<sup>7</sup> group comprises 4 - 9 carbons and at least one N, O, or S heteroatom;

wherein

Y represents O or S;

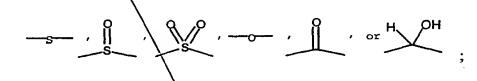
 $R^{1}$ ,  $R^{2}$ , and  $R^{3}$  are as defined above; and

u is 0, 1, or 2; and

-(CH2)<sub>V</sub>ZR<sup>8</sup> wherein

v is 0 or an integer of 1 to 4; and

Z represents



R8 is selected from the group consisting of:

alkyl of 1 to 12 carbons;

aryl of 6 to 10 carbons;

heteroaryl comprising 4 \( \frac{1}{2} \) 9 carbons and at least one N, O, or S heteroatom;

arylalkyl wherein the aryl portion contains 6 to 12 carbons and the alkyl portion contains 1 to 4 carbons;

heteroaryl-alkyl wherein the aryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

-C(O)R<sup>9</sup> wherein R<sup>9</sup> represents alkyl of 2 - 6 carbons, aryl of 6 - 10 carbons, heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, or arylalkyl in which the aryl portion contains 6 - 10 carbons or is heteroaryl comprising 4 -

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9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 4 carbons; and with the provisos that

- when  $R^8$  is  $-C(O)R^9$ , Z is S or O;
- when Z is O,  $R^8$  may also be  $-(C_qH_{2q}O)_rR^5$  wherein q, r, and  $R^5$  are as defined above; and
- \* -(CH<sub>2</sub>)<sub>w</sub>SiR<sup>10</sup><sub>3</sub> wherein
  w is an integer of 1 to 3; and
  R<sup>10</sup> represents alkyl of 1 to 2 carbons;

and with the proviso that

y is 0 - 4; and

- aryl or heteroaryl portions of any of said T or  $R^6$  groups optionally may bear up to two substituents selected from the group consisting of  $-(CH_2)_yC(R^4)(R^3)OH$ ,  $-(CH_2)_yOR^4$ ,  $-(CH_2)_ySR^4$ ,  $-(CH_2)_yS(O)R^4$ ,  $-(CH_2)_yCOR^4$ ,  $-(CH_2$ 

R<sup>3</sup> and R<sup>4</sup> are defined as above, and any two R<sup>4</sup> which are attached to one nitrogen may be joined to form a heterocycle;

and pharmaceutically acceptable salts and prodrugs thereof for the manufacturing of drugs for the treatment and prevention of respiratory diseases.

2. Use of compounds according to claim 1 having matrix metalloprotease inhibitory activity and the generalized formula:

(T)<sub>X</sub>A-B-D-E-CO<sub>2</sub>H

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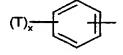
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wherein

(a)  $\backslash$  (T)<sub>X</sub>A represents a substituted or unsubstituted aromatic or heteroaromatic moiety selected from the group consisting of:



and



wherein

each T represents a substituent group, independently selected from the group consisting of:

- \* the halogens -F, -Cl, -Br, and -I;
- \* alkyl of 1 10 carbons;
- \* haloalkyl of 1 10 carbons;
- \* alkenyl of 2 10 carbons;
- \* alkynyl of 2 10 carbons;
- \* -(CH<sub>2</sub>)<sub>p</sub>Q, wherein p is 0 or an integer 1 4,
- \* -alkenyl-Q, wherein said alkenyl moiety comprises 2 4 carbons, and
- \* -alkynyl-Q, wherein said alkynyl moiety comprises 2 7 carbons; and

Q is selected from the group consisting of -OR4 and -SR4;

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R<sup>4</sup> represents H; alkyl of 1 - 12 carbons; aryl of 6 - 10 carbons; de.

heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;

arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons;

heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

 $-C(O)OR^2$ ; or

 $\C(O)R^2$ ;

and with the proviso that unsaturation in a moiety which is attached to Q or which is part of Q is separated from any N, O, or S of Q by at least one carbon atom, and

x is 0, 1, or 2;

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(b) B represents an optionally substituted phenyl or thienyl ring containing 0-2 substituents T, which substituents T may independently have the meaning specified under (a).

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(c) D represents

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(d) E represents a chain of n carbon atoms bearing m substituents R<sup>6</sup>, wherein said R<sup>6</sup> groups are independent substituents, or constitute nonspiro rings in which two groups R<sup>6</sup> are joined, and taken together with the chain atom(s) to which said two R<sup>6</sup> group(s) are attached, and any intervening chain atoms, constitute a 5 or 6-membered ring; and wherein

n is 2 or 3; m is an integer of 1 or 2;

each group R<sup>6</sup> is independently selected from the group consisting of:

- \* arylalkyl wherein the aryl portion contains 6 10 carbons and the alkyl portion contains 1 8 carbons;
- \*  $\sqrt{-(CH_2)_t R^7}$  wherein this 0 or an integer of 1 5; and

R is selected from the group consisting of

wherein

R<sup>2</sup> is independently selected from the group consisting of: H; aryl of 6-10 carbons

-(CH<sub>2</sub>)<sub>V</sub>ZR<sup>8</sup> wherein
 v is 0 or an integer of 1 to 4; and
 Z represents

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-s , s , or H OH

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R<sup>8</sup> is selected from the group consisting of:

alkyl of 1 to 12 carbons;

aryl of 6 to 10 carbons;

heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;

arylalkyl wherein the aryl portion contains 6 to 12 carbons and the alkyl portion contains 1 to 4 carbons;

heteroaryl-alkyl wherein the aryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

-C(O)R<sup>9</sup> wherein R<sup>9</sup> represents alkyl of 2 - 6 carbons, aryl of 6 - 10 carbons, heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, or arylalkyl in which the aryl portion contains 6 - 10 carbons or is heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 -4 carbons;

and with the provisos that

- when  $\mathbb{R}^8$  is  $-\mathbb{C}(0)\mathbb{R}^3$ , Z is S or O;
- when Z is O, R<sup>8</sup> may also be -(C<sub>q</sub>H<sub>2q</sub>O)<sub>r</sub>R<sup>5</sup> wherein q, r, and R<sup>5</sup> are as defined above; and

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-(CH<sub>2</sub>)<sub>w</sub>SiR<sup>10</sup><sub>3</sub> wherein
w is an integer of 1 to 3; and
R<sup>10</sup> represents alkyl of 1 to 2 carbons;

and with the proviso that

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aryl or heteroaryl portions of any of said T or R<sup>6</sup> groups optionally may bear up to two substituents selected from the group consisting of OR<sup>4</sup>, N(R<sup>4</sup>)<sub>2</sub>, -OC(R<sup>4</sup>)<sub>2</sub>O- in which both oxygen atoms are connected to the aryl ring, CON(R<sup>4</sup>)<sub>2</sub>, OCOR<sup>4</sup>, -halogen, -NO<sub>2</sub>, and alkyl with up to 6 carbon atome

wherein

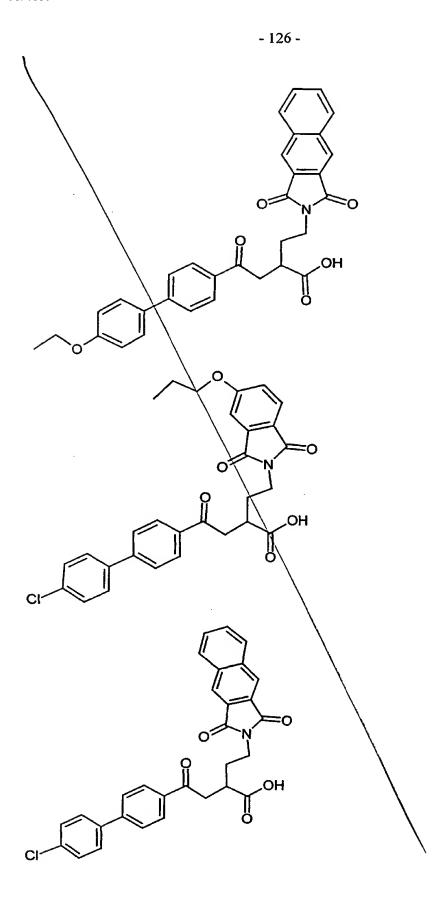
R4 is defined as above;

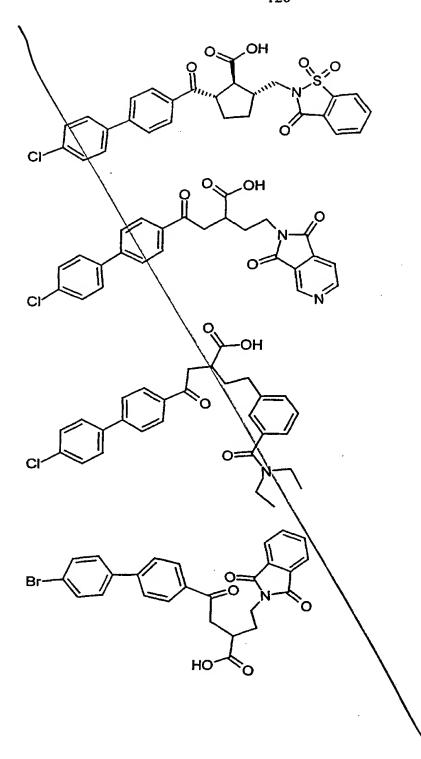
and pharmaceutically acceptable salts and prodrugs thereof for the manufacturing of drugs for the treatment and prevention of respiratory diseases.

- 3. Use of a compound of claim 1 or 2, wherein at least one of the units A, B, T, and R<sup>6</sup> comprises a heteroaromatic ring for the manufacturing of drugs for the treatment and prevention of respiratory diseases.
- 4. Use of a compound of claim 1 or 2, wherein in said E unit, n is 2 and m is 1 for the manufacturing of drugs for the treatment and prevention of respiratory diseases.

5. Use of a compound of claim 1 or 2, wherein A is

- B is p-phenylene and D is a carbonyl group for the manufacturing of drugs for the treatment and prevention of respiratory diseases.
- 6. Use of a compound of claim 1 or 2, wherein the compound is selected from the following group:





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for the manufacturing of drugs for the treatment and prevention of respiratory diseases.

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## 7. Compounds of the general formula (I')

wherein CO-E-CO<sub>2</sub>H represents a 3-carboxyl-5-R<sup>7</sup>-pentan-1-on-1-yl- residue and the substituents T and R<sup>7</sup> have the meaning indicated in the following table:

T	R <sup>7</sup>	racemate, (+)- or (-)- enantiomer	
OEt	>	(+)	;
OEt	>	(-)	,
OAc		rac	;
ОН	- 2	rac	;



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T	R <sup>7</sup>	racemate, (+)- or (-)- enantiomer	
Cl	-N CH <sub>3</sub>	rac	•
Br	->	(+)	;
Br	-N	(-)	,
Cl	->\\	(+)	;
Cl	->	(-)	,
CN	, z-z', z	rac	or
OCF <sub>3</sub>	, N,	rac	·

8. A compound (+)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-(4'-ethoxy[1,1'-biphenyl]-4-yl)-4-oxobutanoic acid

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OH OH

9. Use of compounds of the general formula (I')

T is (C<sub>1</sub>-C<sub>4</sub>)-alk xy, chloride, bromide, fluoride, acetoxy, hydroxy, cyano, trifluoromethyl or trifluoromethoxy,

CO-E-CO<sub>2</sub>H represents a 3-carboxyl-5-R<sup>7</sup>-pentan-1-on-1-yl- or a 2-carboxyl-3-(R<sup>7</sup>-methyl)-cyclopentan-1-yl)carbonyl-residue, and

R<sup>7</sup> represents a group of the formula

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and their salts, for the manufacturing of drugs for the treatment and prevention of respiratory diseases.

10. Use of the compound

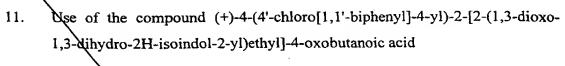
(+)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-(4'-ethoxy[1,1'-biphenyl]-4-yl)-4-oxobutanoic acid,

for the manufacturing of drugs for the treatment and prevention of respiratory diseases.

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for the manufacturing of drugs for the treatment and prevention of respiratory diseases.

- 12. The use of a compound according to any one of claims 1 to 6 or 9 to 11 in the manufacture of a medicament for the treatment of a condition mediated by MMP-2, MMP-3, MMP-9, MMP-12 and/or MMP-13.
- 13. A method of treating or preventing a condition mediated by MMP-2, MMP-3, MMP-9, MMP-12 and/or MMP-13, which comprises administration of an effective amount of a substance according to any one of claims 1 to 6 or 9 to 11.
- Use of a compound according to any one of claims 1 to 6 or 9 to 11 for the treatment and prevention of asthma; chronic obstructive pulmonary diseases including chronic bronchitis and emphysema; cystic fibrosis; bronchiectasis; adult respiratory distress syndrome (ARDS); allergic respiratory disease including allergic rhinitis; diseases linked to TNF<sub>α</sub> production including acute pulmonary fibrotic diseases, pulmonary sarcoidosis, silicosis, coal worker's

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pneumoconiosis, alveolar injury in mammals, such as human, a farm animal or a domestic pet.

15. Use of a composition having matrix metalloprotease inhibitory activity, comprising a compound of any one of claims 1 to 12 and a pharmaceutically acceptable carrier for the manufacturing of drugs for the treatment and prevention of respiratory diseases.

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- 16. Composition containing compounds according to Claim 7 or 8.
- 17. Composition according to Claim 16 for the treatment and prevention of acute and chronic inflammatory processes.